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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,458	09/10/2003	Gary W. Pace	QRX-0300 (15005.105005)	7151

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EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1616	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,458	PACE ET AL.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/5/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/28/09 has been entered.

Claims 1-37 have been cancelled. Claims 38-45 are under examination.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 10/5/09 was filed after the mailing date of the final office action on 4/15/09. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Withdrawn rejections:

Applicant's amendments and arguments filed 9/29/08 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn. Claims 38-45 were rejected under 35 U.S.C. 103(a) as being unpatentable over Mercer, M. Anaesthesia for the Patient with Respiratory Disease (Practical Procedures 2000, 12, 15 pages) in view of Smith et al. (US 6,310,072). A new ground of rejection follows.

Applicant's arguments are moot in view of the new ground of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 38-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (US 6,310,072) and Mercer, M. Anaesthesia for the Patient with Respiratory Disease (Practical Procedures 2000, 12, 15 pages) and Riley et al. (Otolaryngol Head Neck Surg 1997, 117, 648-52) (reference #19 on the IDS filed on 10/5/09).

Applicant claims a method for treating a human with a respiratory illness for the alleviation or prevention of pain, said method comprising administering to the human with the respiratory illness a sub-analgesic dose of morphine or a pharmaceutically

acceptable salt thereof, and a sub- analgesic dose of oxycodone or a pharmaceutically acceptable salt thereof, whereby said treatment produces an analgesic effect in the human and the human experiences a reduced level of respiratory depression than associated with a dosage of morphine or oxycodone required to achieve the same analgesic effect.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Smith et al. teach

> **72**. A method for producing analgesia in humans and lower animals which comprises administering concurrently to a human or lower animal in need of such treatment a composition comprising a sub-analgesic dosage of a μ-opioid agonist selected from the group consisting of morphine, fentanyl, sufentanil, alfentanil and hydromorphone, or a pharmaceutically acceptable salt thereof, and a sub-analgesic dosage of oxycodone which is a κ_2-opioid agonist or a pharmaceutically acceptable salt thereof.
>
> **73**. A method as claimed in claim **72** wherein the μ-opioid agonist is in the form of a pharmaceutically acceptable salt.
>
> **74**. A method as claimed in claim **72** wherein the μ-opioid agonist is morphine.

Smith et al. teach

mg/kg and about 5 mg/kg every three to six hours.

143. A method as claimed in claim **72** wherein the mode of administering the composition is selected from the group consisting of oral, rectal, parenteral, sublingual, buccal, intrathecal, epidural, intravenous, intra-articular, intramuscular, intradermal, subcutaneous, inhalational, intraocular, intraperitoneal, intracerebroventricular and transdermal.

Thus Smith et al. teach producing analgesia, alleviating or preventing pain, in all humans with the composition. Since Smith et al. use the same sub-analgesic amounts as claimed, then the method of Smith et al. intrinsically produces a reduced level of respiratory depression. Smith et al. teach various administration routes, including oral, parenteral, subcutaneous and intravenous, and controlled-release dosage forms reading on instant claim 43 (see claims 143 and 155). It is the Examiner's position, in the absence of evidence to the contrary, that Smith et al. make the distinction between immediate release oral dosing and sustained release oral dosing and thus reads on instant claim 10 and 26-28. Smith et al. teach dosages between about 0.5 and about 3.5 mg morphine and between about 1.0 and about 8.0 mg oxycodone (column lines and column 7, lines 25-30). Thus there can be 1 mg of morphine and 2 mg of oxycodone for a ratio of 1:2 by weight.

Smith et al. teach a wide range of dosages in claims 72-145 reading on instant claims 39-41.

It is the Examiner's position that the "sub-analgesic dosage" of Smith et al. is the same as instantly claimed because Smith et al. define "sub-analgesic dosage" in

column 5, line 47 through column 6, line 8 which is virtually verbatim the same as in [0036] of the USPGPUB of the instant application.

It is intrinsic to the method of Smith et al. that the treatment alleviates or prevents pain and produces an analgesic effect in the human and the human experiences a reduced level of respiratory depression than associated with a dosage of morphine or oxycodone required to achieve the same analgesic effect. Indeed, Smith et al. teach a reduction in undesirable side effects and clearly states in column 24, lines 51-54:

> achieve profound analgesia in humans with a reduced incidence of undesirable opioid side-effects (sedation, respiratory depression) by co-administering appropriate subanalgesic doses of morphine plus oxycodone.

Thus Smith et al. were aware of the respiratory depression that accompanies therapeutic doses. Smith et al. teach, for example, that morphine can be used from about 3 mg to about 21 mg and oxycodone can be used from about 3 mg to about 24 mg which would render obvious at least a ratio of 1:1 (claims 87 and 108). Smith et al. teach a wide range of dosages in claims 72-145. Smith et al. teach in an intravenous route of morphine of 0.01 mg/kg and about 0.04 mg/kg every 4 hours (column 7, lines 4-8) and an oral or parenteral route of oxycodone of between 0.1 mg/kg and about 5 mg/kg every three to six hours (column 8, lines 20-25 but see as well column 6, line 29 through column 8, line 25). Smith et al. teach in claim 143:

mg/kg and about 5 mg/kg every three to six hours.

143. A method as claimed in claim 72 wherein the mode of administering the composition is selected from the group consisting of oral, rectal, parenteral, sublingual, buccal, intrathecal, epidural, intravenous, intra-articular, intramuscular, intradermal, subcutaneous, inhalational, intraocular, intraperitoneal, intracerebroventricular and transdermal.

Smith et al. teach various administration routes and controlled-release dosage (see claim 155).

Please note that the U.S. Patent Office is not equipped with analytical instruments to test prior art compositions for the infinite number of ways that a subsequent applicant may present previously unmeasured characteristics such in instant claims 40 and 41: wherein the combined mass of morphine and oxycodone in the composition is about 50% of the mass of morphine alone required to achieve the same analgesic effect in the patients to which the composition is administered; and wherein the combined mass of morphine and oxycodone in the composition is about 75% of the mass of oxycodone alone required to achieve the same analgesic effect in the patients to which the composition is administered. When as here, the prior art appears to contain the exact same ingredients and applicant's own disclosure supports the suitability of the prior art composition as the inventive composition component, the burden is properly shifted to applicant to show otherwise. It is the Examiner's position that the amount of analgesics will vary with each and every patient as supported by Applicant in the specification at [0037].

Riley et al. teach the use of 1-5 mg of morphine intravenously every 1 to 3 hours and the use of oral oxycodone to provide analgesia in patients with apnea (page 648, Background and page 649, #6). Please note that 1 mg of morphine every 3 hours, which is less than 4 mg of morphine every 4 hours, would be *sub-analgesic* by Applicant's own definition in [0036] of the USPGPUB (see above).

Mercer teaches methods of treating a patient with underlying respiratory disease is at increased risk of postoperative pulmonary complications with opioid analgesics and that pain relief, effective analgesia, reduces the incidence of postoperative respiratory complications, but that respiratory depression is observed for and prevented (pages 1, 2, 10, and 11 of 15). Low doses of opioids in an epidural infusion results in the best analgesia for the fewest side effects (page 11 of 15). Tuberculosis, bronchiectasis pneumonia, emphysema, COPD, infection and asthma are mentioned as restrictive pulmonary diseases and postoperative respiratory problems (pages 4, 6, 7, 8, 11, and 12-14 of 15). Mercer teaches that sleep apnea, a sleep disorder, may lead to post operative airway compromise (page 2 of 15).

Summary:

Fact #1) Smith teaches method of producing analgesia with sub analgesic morphine and oxycodone in all patients and is aware of the respiratory depression associated with opioids.

Fact #2) Riley and Mercer teach using opioid analgesics in patients with respiratory illnesses including sleep apnea.

Fact #3) Applicant has not shown any surprising or unexpected results.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Smith is that Smith do not expressly teach a method of treating the sub-population of humans with a respiratory illness for alleviation or prevention of pain. This deficiency in Smith is cured by the teachings of Riley and Mercer.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method of producing analgesia as taught by Smith et al. for individuals with respiratory illnesses, as suggested by Riley and Mercer and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Smith is directed to method of producing analgesia, alleviating and preventing pain, which is the thrust of the instant invention, and Riley and Mercer provide the nexus teaching using low doses of the opioids in order to avoid adverse side effects such as respiratory depression in the sub population of people with respiratory illnesses. Thus, Smith et al. provide an analgesic method using sub-analgesic amounts of the

compounds which would avoid the respiratory depression taught by Mercer and Riley. The predictable and expected result is providing analgesia to the patient with the respiratory illness.

Regarding the limitations of instant claims 40 and 41, the U.S. Patent Office is not equipped with analytical instruments to test prior art compositions for the infinite number of ways that a subsequent applicant may present previously unmeasured characteristics. When as here, the prior art appears to contain the exact same sub-analgesic amounts of ingredients and applicant's own disclosure supports the suitability of the prior art composition as the inventive composition component, the burden is properly shifted to applicant to show otherwise. With regard to the other respiratory illnesses in claim 44, such illnesses are obvious to one of ordinary skill in the art of respiratory illnesses, in the absence of evidence to the contrary.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments:

Applicant's arguments are moot in view of the new ground of rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 38-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5-11 of copending Application No. 11/544187. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the copending application embraces or is embraced the instant subject matter. Applicant has cancelled the claims that were restricted out of the instant application and added new claims 5-11 in the copending application which are drawn to methods of treating a human with sleep apnea, a respiratory illness, for the alleviation or prevention of pain with sub analgesic doses of oxycodone and morphine. Sleep apnea is a chronic obstructive respiratory sleep disorder which is in instant claims 44 and 45. Therefore,

one of ordinary skill in the art would have recognized the obvious variation of the instant invention over the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (7:15 am-4:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/
Primary Examiner, Art Unit 1616